COVID-19 and TOBACCO: THE UNION MONTHLY BRIEF
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INTRODUCTION

This ninth brief synthesizes the most relevant recent studies, analysing important new research published between the last Union brief (21 December) and today. The team reviewed 116 studies and felt it important to highlight seven epidemiological studies—one is highlighted yellow to indicate it is a pre-print and likely not peer reviewed. The literature review produced two studies (Li et al; Sun et al) worth highlighting primarily because they use new methodology—Li et al. use Mendelian randomization; Sun et al employ unobtrusive observation—to understand the relationship between smoking and advanced COVID-19. Didikoglu and colleagues provide the first evidence on the relationship between maternal smoking and its impact on COVID-19 and hospitalization. There are two studies that address vaping; Li and colleagues examine state-wide e-cigarette use prevalence to determine if there is an association with the number of COVID-19 cases and deaths; Herbec et al. examine adult risk perceptions for severe COVID-19 symptoms to determine if—and how—smokers and vapers believe their health behaviours impact disease symptoms. In their study, Lowe et al. assess the cumulative effect of smoking over time and whether pack-years impacts SARS CoV-2 outcomes. And, the latest "living" study from Simons et al, their tenth to date, shows the same main results from the previous nine meta-analyses.

On the biochemical side, Wang et al. explore a possible new mechanism that may down regulate ACE2, resulting in smokers' potential lower risk for SARS CoV-2 infection.

Please refer to our [main brief](#) for comprehensive definitions of the three COVID-19 disease stages, as well as analysis on the critical questions regarding smoking, infection with SARS-CoV-2, hospital record limitations, biochemistry, and nicotine's alleged protective qualities.

New Methodology

In "Modifiable lifestyle factors and severe COVID-19 risk: a Mendelian randomisation study," Li and Hua [1] selected the genome-wide significant genetic variants associated with lifetime smoking (and other behaviours like body mass index) in up to 941,280 individuals. Using Mendelian randomization—a technique that uses genetic differences to definitively clarify causation—they found that per-standard deviation (SD) increase in genetically predicted lifetime smoking was associated with a nearly two-fold increased risk of severe COVID-19 outcomes. The results significantly bolster previous findings and provide methodologically rigorous evidence that smoking causally increases the risk of severe COVID-19.

Sun et al. [2] conducted an unobtrusive observational study in Hong Kong, examining infection control behaviours at nine outdoor smoking spots. The researchers observed a total of 12,017 smokers, before, during and after COVID-19 outbreaks. They found that 98% of smokers were not wearing a mask while smoking; that 32% did not wear a mask immediately after smoking; and that 74% did not maintain a minimum one metre distance from others. Though it suffers from several limitations—observation times and locations were not uniform in the pre and post COVID periods—this is the first study of its kind and provides important information about how smokers' behaviours increase disease exposure vulnerability.

Maternal Smoking and COVID-19

Using data from the UK Biobank, a longitudinal, population-based cohort of more than half a million UK-based participants aged 37-73 years, Didikoglu et al. [3] examined whether maternal smoking was associated with COVID-19 infection and hospitalization. The researchers ran multivariable logistic regression models on 400,000 participants, adjusting for sex, higher education, average household income, health status, alcohol consumption, and BMI. They found that maternal smoking was positively associated with COVID-19 infection and hospitalization. More specifically, their analysis showed a 20% higher risk of COVID-19 infection among participants whose mothers smoked during pregnancy and a 24% higher risk of COVID-19 hospitalization among participants who experienced maternal smoking. These findings are aligned with a large body of evidence demonstrating the deleterious relationship between maternal smoking and respiratory diseases.

Vaping and COVID-19

Herbec et al [4] analysed data from a cross-sectional study of 2,206 UK adults, examining whether engagement in concurrent health behaviours—smoking and vaping—is associated with risk perceptions for severe COVID-19 symptoms. Participants were asked to classify risk behaviours as either "increasing," "decreasing," or having "no impact" on COVID-19 progression. Smokers and vapers had significantly higher odds of classifying these behaviours as having "no impact" or "decreasing risk"; both groups also had significantly lower odds of classifying these behaviours as "increasing" risk. While this study has not been peer reviewed—and suffers from both a small sample size and cross-sectional design—it may shed important light on media misinformation and mixed messaging that surrounds COVID-19 and health behaviours. It is also possible, of course, that the data are merely representative of "optimism bias" and the tendency to mistakenly believe in one's own invincibility.

With data from the 2018 Behavioural Risk Factor Surveillance System (BRFSS0, the United States Census Bureau, and the 1Point3Acres.com website, Li and colleagues [5] examined the relationship between statewide e-cigarette use prevalence and the number of COVID-19 cases and deaths. They found statistically significant associations between the weighted proportion of vapers and the number of COVID-19 cases and death; with every one percent increase in a state's weighted proportion of vapers, the number of COVID-10 cases increased by 0.31 and the number of COVID deaths increased by 0.37 in log scale. The authors deduct that individual vapers are at increased risk of COVID-19, but we caution against this conclusion. In addition to the fact that this is an ecological study—and one in which population-level associations are inaccurately inferred to the individual level—the authors did not have key data on what proportion of people who contracted COVID-19 or died from it were actually vapers.

Smoking and COVID-19: Pack Years and Meta-analysis

In the first published study on the cumulative effect (measured in "pack years") of smoking on SARS CoV-2, Lowe et al. [6] ran multivariable logistic regression models on 7,000 patients from a hospital system in two U.S. states. For each pack year cohort, they examined the odds ratio for hospitalization given a positive test; ICU admission given hospitalisation; and death given a positive COVID-19 test, comparing each smoker group to never smokers. The findings reveal a dose-response association between pack years and adverse COVID outcomes. When adjusted for three variables—age, race and gender—patients with thirty-plus pack years fared particularly poorly as compared to never smokers: they were 1.89 times more likely to die from COVID-19; 1.69 times more likely to be admitted to the ICU; and had a 2.25 times higher odds of hospitalisation. Because the findings were attenuated when also adjusted for medication and comorbidities, it's likely that COVID-19 extreme outcomes were the result of cumulative pack years plus other health conditions working together. While this study suffers from limitations enumerated in previous briefs—e.g.

reliance on electronic records—it adds to the body of literature demonstrating that smoking produces adverse outcomes in a dose dependent manner.

In their tenth meta-analysis on the relationship between smoking status and SARS CoV-2 infection, hospitalisation, and mortality, Simons and colleagues [7] continue to find the results previously noted. Namely, that current smokers were at reduced risk of infection compared to never smokers; that data on former smokers were inconclusive; and that former smokers—compared to never smokers—were at increased risk of hospitalisation, greater disease severity, and mortality. Data for current smokers across these same inflection points remain inconclusive.

Smoking, Biochemistry and COVID-19

In an effort to understand the underlying mechanisms that appear to put smokers at lower infection risk for SARS CoV-2, Wang et al [8] analysed lung epithelial cells of smoker and non-smoker COVID-19 patients. After determining that cigarette smoke appeared to inhibit infection, they conducted further investigation. They determined that nicotine did not change ACE2 expression but found that BaP and NNK were downregulating ACE2, the principal receptor for SARS CoV-2. Though they could not determine how NNK downregulates ACE2, they found that BaP induces significant upregulation of Skp2, an oncoprotein that plays a pivotal role in cell cycle proliferation and progression. This upregulation degrades ACE2, creating fewer pathways for SARS CoV-2 infection.

References:

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3. Didikoglu, A., et al., *Early life factors and COVID-19 infection in England: A prospective analysis of UK Biobank participants.* Early Human Development, 2021. **155**: p. 105326.
4. Herbec, A.B., Jamie; et al., *Perceived risk factors for severe Covid-19 symptoms and their association with health behaviours: Findings from the HEBECO study.* PsyArXiv, 2021.
5. Li, D., et al., *The association between statewide vaping prevalence and COVID-19.* Preventive Medicine Reports, 2020. **20**: p. 101254.
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7. Simons, D., et al., *The association of smoking status with SARS-CoV-2 infection, hospitalisation and mortality from COVID-19: A living rapid evidence review with Bayesian meta-analyses (version 10).* Qeios, 2021.
8. Wang, G., et al., *Degradation of SARS-CoV-2 receptor ACE2 by the E3 ubiquitin ligase Skp2 in lung epithelial cells.* Frontiers of Medicine, 2021.